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FORMULATION AND DEVELOPMENT OF ACECLOFENAC AND MISOPROSTOL MODIFIED RELEASE OF BILAYER TABLETS

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ABSTRACT

This study focused on developing a bilayer tablet of aceclofenac and misoprostol using a matrix system with swellable polymers for sustained drug release. The formulation included HPMC, Xanthan Gum, and Sodium Carboxy methyl cellulose to achieve a 24-hour controlled release profile. Various sustained release (SR) batches were prepared using the wet granulation technique. The formulations were evaluated for their physical and chemical characteristics, in vitro dissolution, and stability. Drug-excipient interactions were studied using FTIR. The physical characteristics of all formulations were satisfactory. The tablets met official monograph limits for assay, weight variation, hardness, and thickness. In vitro dissolution testing showed that SR formulation F12 achieved a 24-hour release profile, complying with USP standards, particularly with HPMC K100, when compared to the other 11 formulations. Stability studies conducted at room temperature and 40°C/75% RH over three months demonstrated that the tablets remained stable, with physical appearance, dissolution, and assay results within specified limits. The SR tablets of aceclofenac and misoprostol were stable and successfully formulated to reduce administration frequency and improve patient compliance.

KEYWORDS: Aceclofenac, Misoprostol, Modified Release, Bilayer Tablet.

1. INTRODUCTION

Oral drug delivery is the most convenient and widely used route of administration among all the routes. Discovery and development of new drug candidates, it remains the preferred route

of administration. Popularity of oral route is due to its ease of administration, patient acceptance, cost effective manufacturing methods, accurate dosing, and improving shelf life of a product. The oral solid dosage forms such as tablets and capsules has been formulated and developed nowadays since they are most effective routes of administration of a new drug formulation. Now available pharmaceutical products which are designed for oral delivery over the counter markets are mostly immediate release types of formulations. Which are meant to be immediate release of drug for rapid absorption. Most of many new generations of pharmaceutical products like controlled and sustained release drug delivery systems have also been developed nowadays for improving therapeutic action of a drug molecule. We achieve excellent and effective therapeutic action it will be very much useful to combine the immediate response and maintaining the duration of action of drug over a long period of time frequency level.

1.1 Matrix Tablet

Matrix tablets may be defined as the "oral solid dosage forms in which the drug or active ingredient is homogeneously dispersed throughout the hydrophilic or hydrophobic matrices which serves as release rate retardants". These are the type of controlled drug delivery systems, which release the drug in continuous manner by both dissolution controlled as well as diffusion controlled mechanisms. To control the release of the drugs, which are having different solubility properties, the drug is dispersed in swellable hydrophilic substances, an insoluble matrix of rigid non swellable hydrophobic materials or plastic materials.

1.2 Bilayer Tablet

Bilayer tablets are the medicines which consist of two same or different drugs combined in a single dose for effective treatment of the disease. The aim of this review is to reveal the challenges that appear during the preparation of bilayer tablets, and also propose solutions for these challenges. Bi-layer tablet is a new era for successful development of controlled release formulation along with various features to provide successful drug delivery. Bi-layer tablets can be primary option to avoid chemical incompatibilities between APIs by physical separation and to enable the development of different drug release profiles. Bi-layer tablet is suitable for sequential release of two drugs in combination and also for sustained release of tablet in which one layer is for immediate release as loading dose and second layer is maintenance dose.

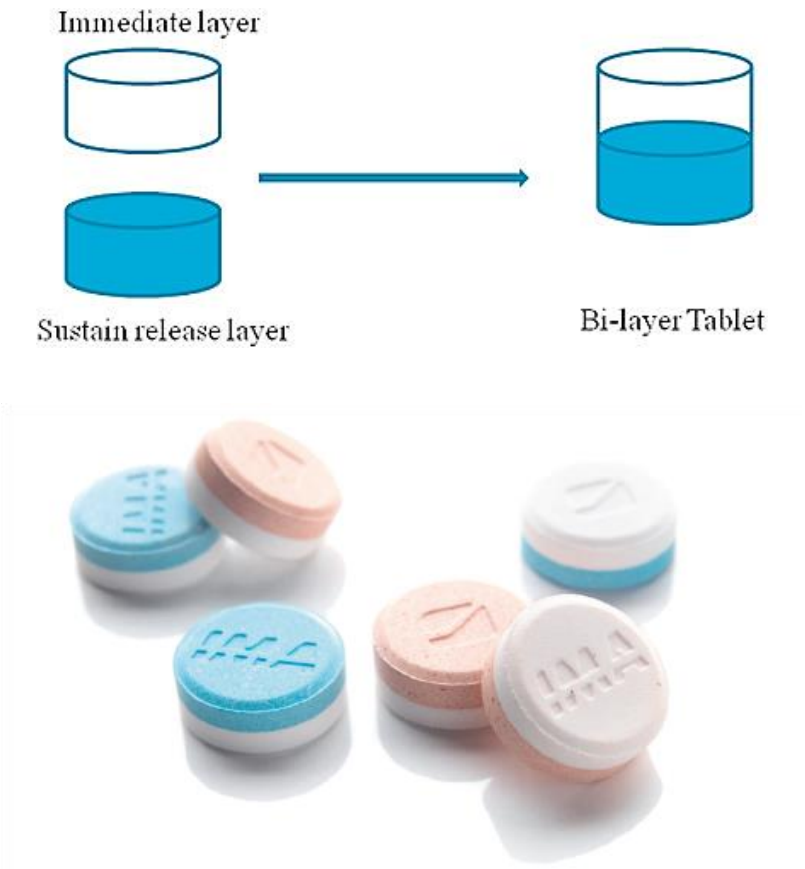

Fig: 1 Bilayer Tablet.

2. DRUG PROFILE

2.1 Aceclofenac

Aceclofenac is a medicine called a non-steroidal anti-inflammatory drug. It is also known as 'an NSAID'. Before you take aceclofenac, tell your doctor if you have ever had an allergic reaction to any other anti-inflammatory painkiller. Take one tablet in the morning and one in the evening.

Aceclofenac ($C_{16}H_{13}Cl_2NO_4$), chemically [(2-{2, 6-dichlorophenyl) amino} phenylacetooxyacetic acid], is a crystalline powder with a molecular weight of 354.19. It is practically insoluble in water with good permeability. It is metabolized in human hepatocytes and human microsomes to form [2-(2',6'-dichloro-4'-hydroxy- phenylamino) phenyl] acetoxyacetic acid as the major metabolite, which is then further conjugated. According to the Biopharmaceutical Classification System (BCS) drug substances are classified to four classes upon their solubility and permeability. Aceclofenac falls under the BCS Class II, poorly soluble and highly permeable drug.

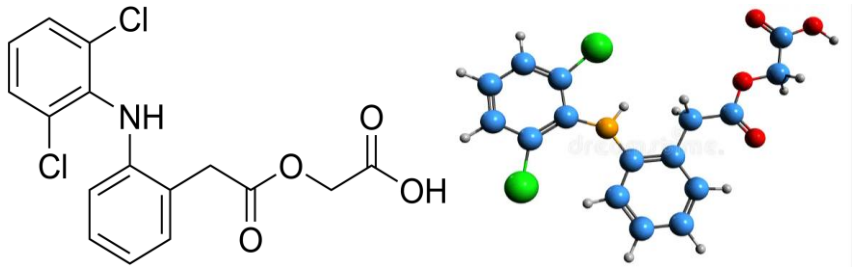

Fig 2: Structure Of Aceclofenac.

2.2 Misoprostol

Misoprostol is a synthetic prostaglandin medication used to prevent and treat stomach and duodenal ulcers, induce labor, cause an abortion, and treat postpartum bleeding due to poor contraction of the uterus. Misoprostol is taken by mouth when used to prevent gastric ulcers in persons taking NSAIDs.

Misoprostol ($C_{22}H_{38}O_5$) with a molecular weight of 382.53, It is metabolized in human Liver (extensive to misoprostic acid). According to the Protein binding 80–90% (active metabolite, misoprostol acid). If you are taking this drug to prevent stomach ulcers, take it by mouth usually four times a day, after meals and at bedtime to minimize diarrhea, or as directed by your doctor. If you are taking this medication for abortion, take it by mouth exactly as directed by your doctor. If you are using this medication to start labor, your healthcare professional will insert it into your vagina. Avoid taking antacids that contain magnesium while using misoprostol because they may make the diarrhea it causes worse. If you need an antacid, consult your doctor or pharmacist to help you choose a product. For ulcer prevention, continue to take this drug for as long as you take NSAIDs. Use this medication regularly in order to get the most benefit from it. Remember to use it at the same times each day. Inform your doctor if your condition persists or worsens.

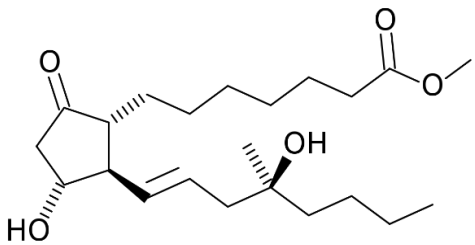

Fig: 3 Structure Of Misoprostol.

3. MATERIALS AND METHODS

3.1 Raw Materials Analysis

3.1.1 Description: Appearance of the materials was noted, compared with specified monograph or with standard materials.

3.1.2 Identification: Identification is the important parameter for Qualitative Analysis of materials. Material was identified by chemical and FT-IR method.

3.1.3 Solubility Analysis: Solubility is an important parameter for preformulation studies because: It affects the dissolution of drug. Bioavailability of drug is directly affected by dissolution and absorption of drug by oral administration. Particle size, shape, surface area may affects the dissolution characteristics of drug hence it should be determined during preformulation.

3.1.4 Loss on drying (%): 1g of drug was accurately weighed and dried in an oven at 105°C for 3 hours. By gentle sidewise shaking, the sample was distributed at the specified temperature for constant weight. The drug sample was allowed to come to room temperature in a desiccator before weighing. The difference between successive weights should not be more than 0.5mg.

3.1.5 Melting point determination: The melting point of active ingredients were determined by capillary method, by using definite quantity of active ingredients which were taken and placed in apparatus and melting point was determined and matched with standards.

3.2 Pre-formulation Studies

It is one of the important prerequisite in development of any drug delivery system. Preformulation studies were performed on the drug, which included melting point determination, solubility and compatibility studies.

3.2.1 Fourier transform infrared spectroscopy (FTIR)

In order to check the integrity (Compatibility) of drug in the formulation, FT-IR spectra of the formulations along with the drug and other excipients were obtained and compared using Shimadzu FT-IR 8400 spectrophotometer. In the present study, Potassium bromide (KBr) pellet method was employed. The samples were thoroughly blended with dry powdered potassium bromide crystals. The mixture was compressed to form a disc. The disc was placed in the spectrophotometer and the spectrum was recorded. The FT-IR spectra of the formulations were compared with the FT-IR spectra of the pure drug and the polymers.

3.2.2 Bulk density

The bulk density also called as poured density. It is usually measured by passively filling in measuring vessel.

Procedure

Pass the sample through 18 mesh to break the agglomerates that may formed during storage. Weigh the sample around 100gm and then fill the powder into a 250ml measuring vessel. Measure the volume (V_0).

Bulk density (ρb) = M/V_0

Where,

M = Mass of the powder in gm

V_0 = Volume of the powder in ml

3.2.3 Tapped density

The tapped density is the density measured by mechanically tapped measuring cylinder which contains materials in it. Tested by using tap density tester.

Procedure

Weigh and fill the material into a cylinder, note the volume(V_0) and tap the material at the height of 14±2 with its own weight at the rate of 300 taps per min. Tap the cylinder 500 times initially, note the volume (V_a) and again tap the cylinder 750 times, note the volume(V_b). If difference between V_a and V_b is less than 2%, then stop the test and take V_b as the final volume (V_f) or if it is more than 2% again tap the cylinder 1250 times, note the volume (V_c) and take V_c as the final volume (V_f).

Tapped density (ρt) = M/V_f

Where,

M = Mass of the powder in gm.

V_f = Final volume of the powder in ml.

3.2.4 Compressibility index or Carr's Index (CI)

It is useful to find out the powder flow indirectly. It is expressed in percentage and calculated by the formula mentioned below.

$$CI = \frac{(\rho t - \rho b)}{\rho t} \times 100$$

Where,

ρt = Tapped density of a powder.

ρb = Bulk density of a powder.

3.2.5 Hauser's ratio

It is the measure of porosity of a powder to be compressed and also it's inter particulate interactions. The ideal range should be 1.2 to 1.5 and calculated by the formula mentioned below.

HR = ρt /ρb

Where,

ρt = Tapped density of a powder.

ρb = Bulk density of a powder.

3.2.6 Angle of repose (θ)

It is a character related to inter particulate friction or resistance to movement between particles. It is to characterize the flow property of solids. It is defined as the maximum angle possible between the surface of a pile of powder and the horizontal plane. It is determined by fixed funnel method and calculated by the formula mentioned below.

θ= tan-1 (h/r)

Where,

θ = Angle of repose in degrees

h = Height of the pile of powder in cm

r = Radius of the pile of powder in cm

3.2.7 Moisture content

Take 2.5 to 3.5g of granules and observe the moisture content in moisture balance. Note the percentage of moisture content as displayed in the balance.

3.2.8 Drug Content: For Aceclofenac

Weigh accurately a Aceclofenac, shake with 70ml of Phosphate buffer 6.8 for 15 minutes, make up to 100ml with Phosphate buffer 6.8, and filter. Dilute 10ml of the filtrate to 100ml with Phosphate buffer 6.8. Further 10ml of the filtrate were make up to 100ml with Phosphate buffer 6.8 and measure the absorbance of the resulting solution at the maximum about 276nm.

3.3 Post Compression Studies Of Tablets

3.3.1 Description

The general appearance of a tablet including size, shape, colour, having score or not, coated or uncoated, should be observed. It is must to have a good appearance for consumer acceptance. Physical changes may occur during storage, which can be determined easily by matching with the description.

3.3.2 Weight variation

Weigh individually 20 tablets, which were taken randomly and determine the average weight. Not more than 2 of the individual tablets weight should not deviate from the weight variation limits.

3.3.3 Thickness

It can be dimensionally described & controlled. Thickness may affect the hardness, and dissolution rate. Tablet thickness can be measured by using callipers, and it should be measure at least for six tablets.

3.3.4 Diameter

It is also dimensionally described & controlled. Tablet diameter can be measured by using dial calliper. It also should measure for six tablets in general.

3.3.5 Hardness

Tablet requires certain amount of strength or hardness to withstand mechanical shocks occur during handling in manufacture, packing and shipping. Strength of the tablet was expressed as tensile strength (Kg/cm2). The tablet crushing load is the force, which is required to break a tablet. Six tablets have to take from each batch, and the average hardness has to be determined by using Monsanto hardness tester.

3.3.6 Friability

Take few tablets of a weight as near as possible to 6.5 gm. Those tablets should be carefully de-dusted prior to testing. Accurately weigh the tablet sample and note the weight ($W_{initial}$) and place the tablets in the drum. Rotate the drum 100 times at 25±2 rpm and remove the tablets. Again de-dust the tablets as before and weigh accurately, note the value (W_{final}).

3.3.7 *In vitro* dissolution studies

The study was carried out for 24 hours. 5ml of samples were withdrawn on time interval of 1,6 and 12th hour and replaced with fresh medium. Samples were filtered, diluted and absorbance was measured at 276 nm (Aceclofenac) & 237 nm (Misoprostol) using UV-VIS Spectrophotometer.

Apparatus	**:**	USP Type II (Paddle type)
Medium	**:**	Phosphate Buffer 6.8 & 0.1 N HCl
Rpm	**:**	75
Volume	**:**	900 ml
Temp	**:**	37 ± 0.5ºC

3.3.8 Evalution of *Invitro* release kinetics

To study kinetics, data obtained from in vitro release were plotted in various kinetic models.

1. Zero order equation: $C=K_0t$
2. First order equation: Log C = log C_0-Kt /2.303
3. Higuchi kinetics: $Q = Kt^{1/2}$
4. Korsmeyer – Peppas equation: $M_t /M_\infty = Kt^n$

3.4 Stability Study

Stability of a pharmaceutical preparation can be defined as "the capability of a particular formulation in a specific container/closure system to remain within its physical, chemical, microbiological, therapeutic and toxicological specifications throughout its shelf life."

3.5 Formulation Of Bilayer Tablet

3.5.1. Procedure for IR

Sieving

Sift total dispensed quantity of Misoprostol in HPMC along with croscarmellose sodium through 40-mesh (420µm) and collected. Sift total dispensed quantity of Crospovidone through 40 mesh and collected. Sift total dispensed quantity of MCC (Vivapur 12) along with Sunset yellow lake through 40- mesh (420µm) and collected. Total dispensed quantity of Magnesium stearate (Lubrication) sifted through 40-mesh (420µm) and collected into a poly bags appropriately labeled.

Blending & Lubrication

Transfer the sifted materials into nearby blender-200 lits. Added the total quantity of sifted materials Misoprostol 1% HPMC along with croscarmellose sodium, MCC along with sunset yellow lake, Crospovidone into the blender for 15 minutes at 10 RPM. The above pre-Blend again sifted through 40 # sieve and collected into bag. Load total quantity of above sifted pre blend into bin and seal blender bin and mix for 10 minutes at 10 RPM. Add total quantity of sifted (40 # mesh) Magnesium Stearate to the above blender bin and mix for 5 minutes at 10 RPM. Store the lubricated granules in IPC lined with double poly bag with product identity, manufacture date, batch number and quantity. Until required for tableting, the lubricated granules is stored in a secure holding area NMT 26℃ and RH should be not more than 60%. Maximum hold time of lubricated granules is NMT 7 days from date of lubrication.

3.5.2. Procedure for SR

Sieving: (Dry Mix part)

Sift separately lot wise quantity of Aceclofenac, HPMC K100M, MCC, sodium Carboxy methyl cellulose through 40# sieve and transfer to RMG by using Pneumatic transfer system.

Sieving: (Lubrication part)

Sift total dispensed quantity of HPMC K4M (Extra granular), Magnesium stearate through 40 mesh (420µm) sieve and collect into a clean double bag. Sift total dispensed quantity (Extra granular) of talc along with colloidal silicon dioxide through 40-mesh (420µm) sieve and collected.

Binder Solution Preparation

In a suitable stainless steel vessel fitted with stirrer, add Isopropyl alcohol and purified water and mix well and start continuous stirring with required RPM to form a vortex. Add separately lot I & II quantity of Povidone slowly into the vortex to form a viscous solution.

Blending & Lubrication

Transfer the IPC bin containing Aceclofenac layer granules into blending area. Transfer the granules (dried & sized granules) into the Double cone blender and seal the blender bin and blend for 5 minutes at 10 RPM Transfer the total quantity of (sifted through 40 # mesh) HPMC K4M, talc with colloidal silicon dioxide into Blender Bin by using pneumatic transfer system and seal the blender bin and mix for 15 minutes at 10 RPM. Transfer the total quantity of sifted (40 # mesh sieve) Magnesium Stearate to the above blender bin by using pneumatic

transfer system and seal the blender bin and mix for 5 minutes at 10 RPM. Unload and Store the lubricated granules in IPC bin and labeled with the product identity, manufacture date, batch number and quantity. Until required for tablet, the bulk lubricated granules is stored in a secure holding area NMT 26℃ and RH should be not more than 60%.

3.5.3. Compression

Set the compression machine with 9.55 mm round shaped shallow concave punches and dies. Allow the lubricated granules to flow into the machine and start the machine. If required pre compression force also apply for the tablet compression. Continue compression after setting all the quality parameters. Pass the compressed tablets through de-duster and metal detector. Limit of Machine speed: 10 RPM to 30 RPM. Collect the tablets in clean IPC/Bulk containers lined with double black poly bag. Check the proper functioning of the metal detector at the start and end of compression.

Table 1: Formulation Table.

RAW MATERIALS	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
MISOPROSTOL	10	10	10	10	10	10	10	10	10	10	10	10
STARCH IP	37	37	35	25	-	-	-	-	-	-	-	-
CROSCARMELLOSE SODIUM IP	5	-	7	7	5	5	5	5	5.5	5.5	5.5	5.5
MICROCRYSTALLINE VIVAPUR 12	25	-	-	35.5	55.5	56.5	-	54.5	-	54.5	52.5	52.5
MICROCRYSTALLINE PH 101	-	30	25	-	-	-	56.5	-	54.5	-	-	-
CROSPOVIDONE IP	-	-	-	-	5	5	5	7.5	7.5	7.5	10	10
SUNSET YELLOW LAKE HIS	1	1	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
MAGNESIUM STEARATE IP	1	1	1.5	2	2	1.5	1.5	-	2	1	1.5	1.8
COLLOIDAL SILICON DIOXIDE IP	-	1	-	-	2	-	-	1.5	-	1	-	-
TALC IP	1	-	1	-	-	1.5	1.5	1	-	-	-	-
TOTEL	80	80	80	80	80	80	80	80	80	80	80	80
ACECLOFENAC	200	200	200	200	200	200	200	200	200	200	200	200
HYDROXY PROPYL METHYL CELLOUSE IP	25	25	30	30	30	35	35	40	40	40	40	40
MICROCRYSTALLINE CELLULOSE IP	25	25	20	15	10	5	-	-	8	8	8	5
SODIUM CARBOXY METHYL CELLULOSE IP	10	-	2	5	10	5	2	5	5	6	-	-
XANTHAM GUM	-	10	5	4	5	15	20	10	-	-	6	8
POVIDONE IP K-30	5	5	5	5	5	5	5	5	5	-	-	-
POVIDONE IP K-90	-	-	-	-	-	-	-	-	-	5	5	5

COLLOIDAL SILICON DIOXIDE IP	**1**	**2**	**2**	**1**	**2**	**-**	**2**	**2**	**2**	**1**	**1**	**2**
MAGNESIUM STEARATE	**2**	**1.5**	**3**	**5**	**4**	**2.5**	**3**	**4**	**5**	**5**	**5**	**5**
TALC IP	**2**	**1.5**	**3**	**5**	**4**	**2.5**	**3**	**4**	**5**	**5**	**5**	**5**
TOTEL	**270**	**270**	**270**	**270**	**270**	**270**	**270**	**270**	**270**	**270**	**270**	**270**

4. RESULTS AND DISCUSSION

4.1 Raw Material Analysis

Solubility Analysis

- Aceclofenac freely soluble in water, insoluble in Methanol.
- Misoprostol freely soluble in ethanol.

4.2 Pre-formulation study of Aceclofenac and Misoprostol

Description

- **Aceclofenac –** Orange color powder, White in Colour and odourless.
- **Misoprostol** – Crystalline powder, White in Colour and odourless.

Solubility

- Freely soluble in water, 0.1N HCl and pH 4.5 Acetate buffer.
- Soluble in pH 6.8 phosphate buffer and pH 7.5 phosphate buffer.

Table 2: Result of Pre-formulation study of Aceclofenac and Misoprostol.

Drug	Angle of Repose (Theta)	Loose bulk density (g/mL)	Tapped bulk density(g/mL)	Carr's index (%)	Hausner's Ratio
Aceclofenac	33.37	0.555	0.667	16.792	1.202
Misoprostol	31.22	0.431	0.532	14.146	0.931

4.3 Drug Content

Linearity Of Aceclofenac In Phosphate Buffer PH 6.8.

Table 3: Linearity Of Aceclofenac In Phosphate Buffer PH 6.8.

S.NO	CONCENTRATION (µg / ml)	ABSORBANCE (nm)
1	10	0.072
2	20	0.123
3	30	0.179
4	40	0.245
5	50	0.295
6	60	0.353
7	70	0.429
8	80	0.478
9	90	0.531
10	100	0.575

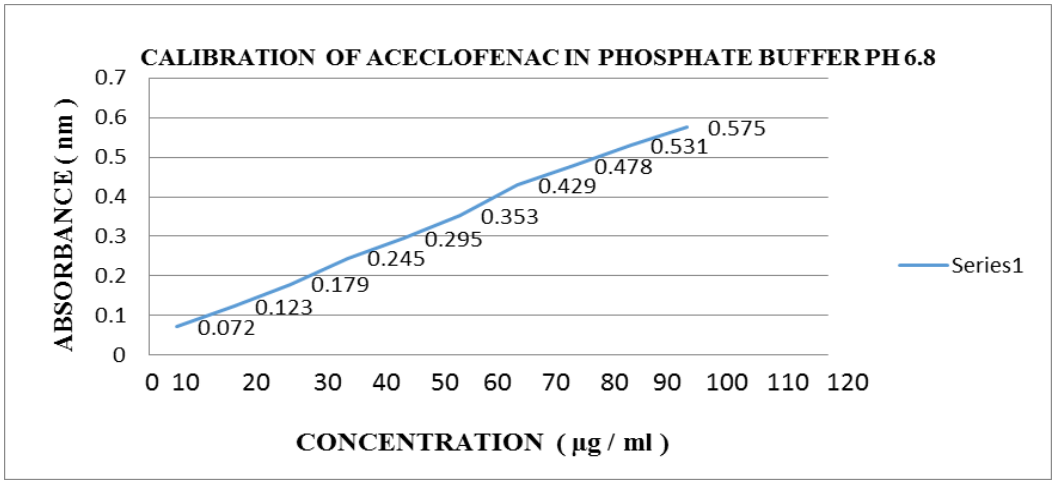

Fig 4: Linearity Of Aceclofenac.

4.4 FT-IR Study

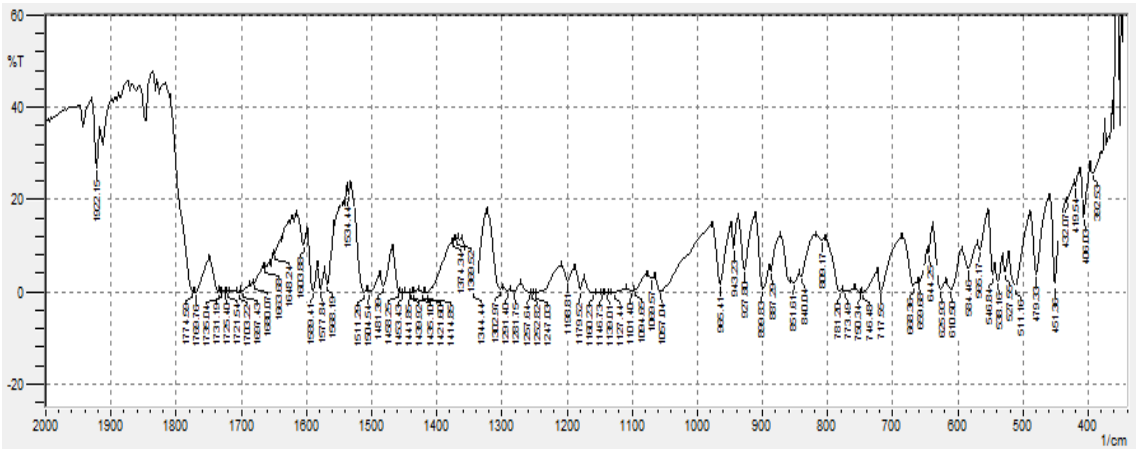

Fig: 5 IR Spectrum Of Aceclofenac.

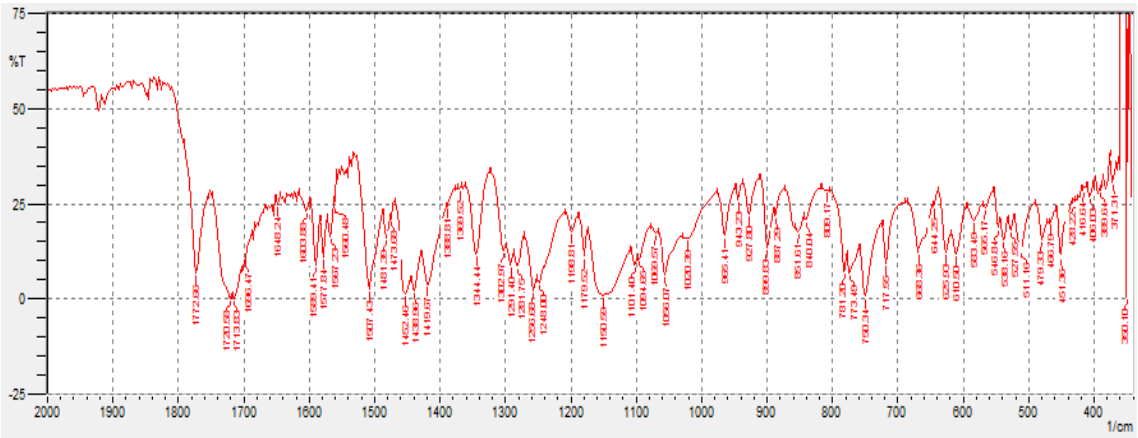

Fig: 6 IR Spectrum Of Aceclofenac With Excipients.

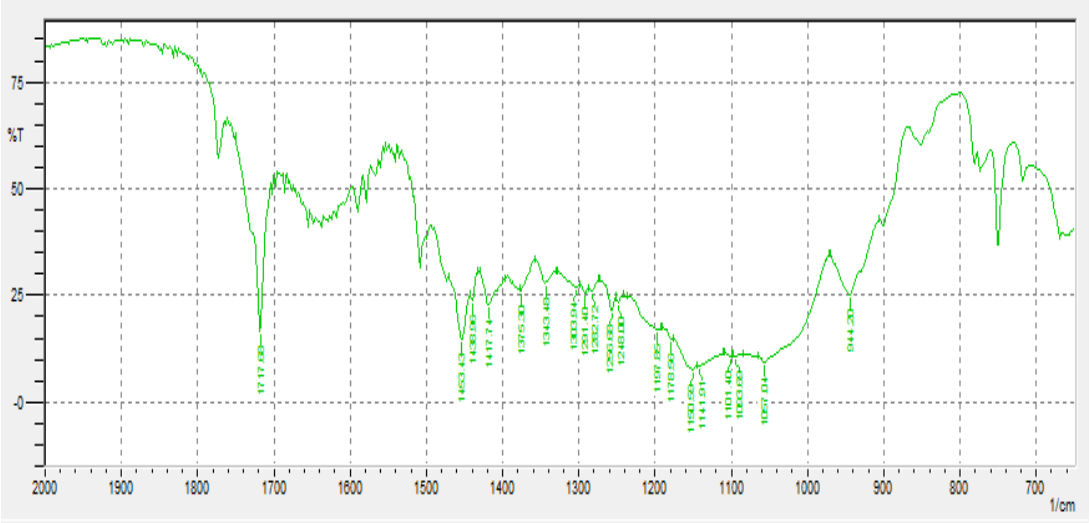

Fig: 7 IR Spectrum Of Misoprostol.

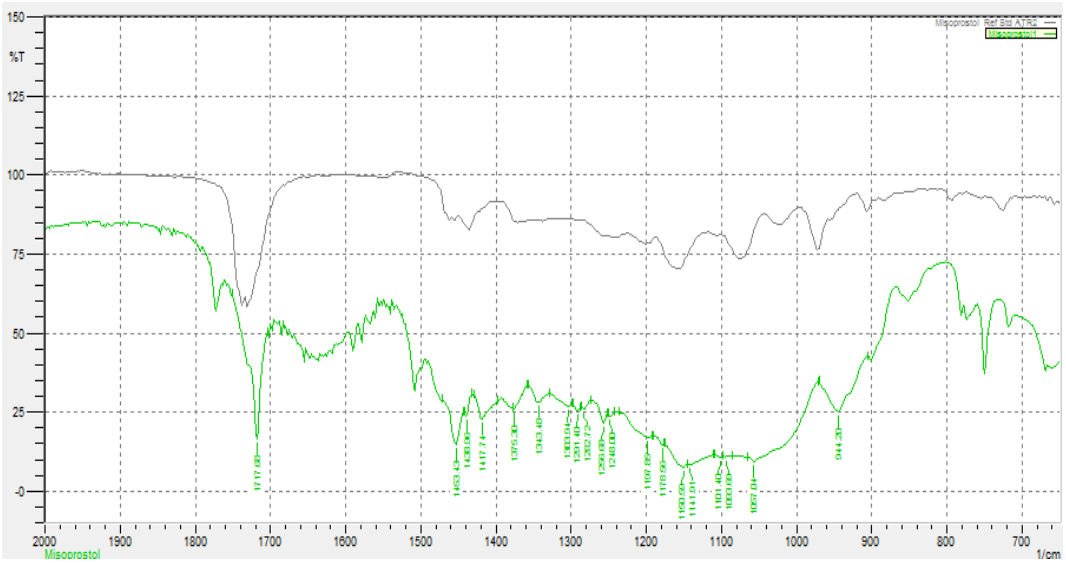

Fig: 8 IR Spectrum Of Misoprostol With Excipients.

4.5 Pre-compression Study

Table 4: Pre-compression study of Aceclofenac.

F	Bulk density* g/cm3	Tapped density* g/cm3	Compressibility index* g/cm3	Hauser's Ratio*	Angle of Repose*	Moisture Content* %w/w
F_1	0.494±0.002	0.623±0.003	20.70±0.606	1.256±0.005	31°76´±0.01	3.16±0.01
F_2	0.486±0.002	0.618±0.004	21.35±0.185	1.266±0.005	32°76´±0.01	2.94±0.01
F_3	0.466±0.003	0.584±0.002	20.20±0.686	1.246±0.011	33°02´±0.02	3.76±0.02
F_4	0.474±0.002	0.598±0.002	20.73±0.310	1.256±0.005	33°20´±0.02	3.88±0.01
F_5	0.536±0.002	0.704±0.002	23.86±0.500	1.310±0.010	32°04´±0.02	3.40±0.02
F_6	0.547±0.001	0.714±0.002	23.38±0.355	1.300±0.010	32°03´±0.01	3.42±0.01
F_7	0.569±0.002	0.718±0.002	20.75±0.255	1.256±0.005	32°36´±0.01	3.46±0.02
F_8	0.560±0.002	0.719±0.001	22.11±0.390	1.280±0.010	32°70´±002	3.82±0.02

F9	0.467±0.003	0.513±0.002	20.20±0.686	1.244±0.011	32°76´±0.01	2.91±0.01
F10	0.481±0.002	0.544±0.002	20.78±0.550	1.256±0.005	33°02´±0.02	3.66±0.02
F11	0.538±0.002	0.688±0.002	21.85±0.330	1.318±0.010	33°20´±0.02	3.98±0.01
F12	0.511±0.001	0.699±0.002	23.31±0.309	1.233±0.011	32°04´±0.02	3.12±0.02

Table 5: Pre-compression study of Misoprostol.

F	Bulk density* g/cm3	Tapped density* g/cm3	Compressibility index* g/cm3	Hauser's Ratio*	Angle of Repose*	Moisture Content* %w/w
F_1	0.326±0.002	0.598±0.003	21.30±0.504	1.154±0.003	30°44´±0.01	3.96±0.01
F_2	0.398±0.002	0.594±0.004	21.33±0.175	1.233±0.003	31°76´±0.01	3.94±0.02
F_3	0.396±0.003	0.584±0.002	22.21±0.606	1.213±0.017	32°08´±0.02	3.96±0.01
F_4	0.413±0.002	0.599±0.002	21.03±0.316	1.211±0.008	32°22´±0.02	3.11±0.01
F_5	0.456±0.002	0.656±0.002	23.86±0.500	1.500±0.010	33°01´±0.02	3.11±0.02
F_6	0.513±0.001	0.675±0.002	23.18±0.335	1.200±0.010	34°02´±0.01	3.47±0.01
F_7	0.500±0.002	0.707±0.002	20.72±0.215	1.306±0.005	31°33´±0.01	3.49±0.02
F_8	0.544±0.002	0.711±0.001	22.10±0.391	1.220±0.010	30°70´±001	3.82±0.02
F9	0.448±0.003	0.691±0.002	20.29±0.786	1.301±0.011	31°72´±0.01	2.91±0.01
F10	0.567±0.002	0.532±0.002	20.78±0.530	1.284±0.008	31°11´±0.01	3.64±0.02
F11	0.601±0.002	0.631±0.002	21.85±0.352	1.309±0.010	31°20´±0.02	3.91±0.02
F12	0.531±0.001	0.644±0.002	23.44±0.398	1.333±0.010	31°03´±0.02	3.11±0.01

4.6 Post-compression Study

Table 6: Post-compression study.

Formulation	Weight variation**	Hardness*	Thickness*	Friability*
F_1	350.6±0.491	4.75±0.05	3.48±0.02	0.200±0.002
F_2	349.8±0.376	4.25±0.25	3.42±0.01	0.175±0.001
F_3	350.4±0.516	4.02±0.02	3.64±0.02	0.205±0.005
F_4	350.6±0.204	4.50±0.05	2.63±0.01	0.102±0.002
F_5	350.4±0.273	4.63±0.10	2.62±0.02	0.107±0.001
F_6	350.2±0.375	5.56 ±0.02	2.33±0.03	0.101±0.001
F_7	348.8±0.204	5.75±0.05	2.54±0.02	0.109±0.003
F_8	349.4±0.258	5.50±0.50	2.47±0.01	0.110±0.001
F9	350.1±0.231	4.11±0.10	2.55±0.02	0.115±0.004
F10	350.2±0.366	4.33 ±0.02	2.78±0.03	0.105±0.001
F11	349.3±0.114	4.75±0.05	2.13±0.02	0.109±0.001
F12	350.4±0.811	6.50±0.50	2.43±0.01	0.111±0.001

4.7 In-vitro Dissolution Study

Table 7: Dissolution Study.

Time in hours	30 min	4^{th} hour	8^{th} hour	24^{th} hour
F_1	29.19±0.02	45.33±0.01	75.39±0.03	93.94±0.02
F_2	33.98±0.01	51.11±0.02	80.82±0.02	96.24±0.04
F_3	19.55±0.05	44.43±0.02	60.44±0.02	94.47±0.02
F_4	17.86±0.02	39.64±0.02	55.64±0.02	85.03±0.01
F_5	29.31±0.01	51.65±0.03	75.65±0.03	98.92±0.02

F_6	22.75±0.05	45.71±0.02	69.71±0.02	94.22±0.02
F_7	19.67±0.01	39.83±0.03	65.83±0.03	95.20±0.05
F_8	22.42±0.02	43.60±0.05	60.60±0.05	97.39±0.03
F9	20.49±0.05	41.40±0.02	69.43±0.02	91.07±0.03
F10	19.81±0.03	44.04±0.03	77.64±0.03	96.01±0.03
F11	31.31±0.01	50.88±0.03	73.61±0.02	93.11±0.02
F12	20.44±0.04	48.69±0.03	73.69±0.02	99.31±0.06

The *In vitro* dissolution release profile of various formulations was studied. The results of *in vitro* dissolution studies of Sustained release formulations, observed that the formulation F12 having a release profile up to 24 hours. It was selected for formulation of sustained release tablet among from formulations F1 to F12. Concluded that the drug release from tablet by the combination of polymers HPMC K_{100}M, Sodium Caroboxymethylcellulose and Guar Gum shows the better release rate profile. Release time also increases with polymer concentration also increased. HPMC K_{100} M along with xantham Gum , microcrystalline cellulose shows the release up to 24 hours.

4.8 Pharmacokinetics Drug Release.

Table 8: Pharmacokinetics Drug Release.

Formulation	Zero Order	First Order	Higuchi	Kors - Peppas
F12	0.9945	0.956	0.9345	0.8719

4.9 Stability Studies

Table 9: Stability Study at 40 º C / 75% RH.

Parameters	1st Month		2nd Month		3rd Month	
	RT	40^0C	RT	40^0C	RT	40^0C
Uniformity of Weight**	350.55±1.52	350.45±1.23	350.45±1.23	350.54±2.12	350.45±1.23	350.54±2.12
Thickness*	3.48±0.087	3.38±0.076	3.38±0.099	3.40±0.191	3.38±0.076	3.35±0.191
Friability*	0.12±0.034	0.12±0.044	0.12±0.065	0.13±0.298	0.12±0.044	0.13±0.298

Table 10: Tablet at stability Study at 40 º C / 75% RH, Assay and Dissolution profile.

Intervals in Months RT	% Drug content*		% Cumulative Release *	
	RT	40°C	RT	40°C
1st month	99.31±0.06	100.98±0.789	97.41±.94	97.86±0.43
2nd month	99.01±0.06	99.31±0.06	97.39±0.809	97.28±1.490
3rd month	98.98±0.05	99.31±0.06	97.48±1.43	97.41±1.394

*Mean ± SD (n=6)

5. CONCLUSION

The Current research study focused towards the development of aceclofenac and misoprostol bilayer tablet. In formulation matrix system was based on swellable polymer which is essential for sustaining the drug release pattern. HPMC, Xantham Gum and Sodium Caroboxy methyl cellulose helps to get the predetermined release profile over a period for 24 hours. Various types of sustained release (SR) batches were formulated by wet granulation technique.

The formulations were evaluated for physical chemical characteristics, in vitro dissolution study and stability study. Below the conclusions have been made from the present study method.

- Prospect of Drug – Excipients interaction was investigated by FTIR of analytical method.
- Physical characteristics of all the blended formulations were adequate.
- Primed tablets evaluated for assay, weight variation, hardness and thickness were found to be within the official monograph limits.
- Tablet *In Vitro* Dissolution study of SR formulations F12 showed release profile for 24 hours which complies with USP at a certain concentration of $HPMCK_{100}$ when compared with other 11 formulations.
- Stability studies were conducted for 3 months at room temperature and 40°C/75% RH. After the duration, the product was analyzed for physical appearance, dissolution study and assay profile. We got the results were found to be within the predetermined specification limits.
- The formulated SR tablets containing of aceclofenac and misoprostol were found to be stable nature. Hence, to reduce the frequency of administration and to improve the patient compliance, SR tablets were successfully formulated and evaluated.

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